

# A New Approach to the Resection of Pulmonary Osteosarcoma Metastases

## Results of Aggressive Metastasectomy

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Pulmonary metastases are the primary cause of death from bone and soft-tissue sarcoma. Recognition that even multiple resections of metastases can improve survival has led to a more aggressive surgical approach to these patients. The authors instituted an aggressive approach and a new technique and retrospectively analyzed the results of multiple, pulmonary metastasectomies for pulmonary metastases in 34 patients, 21 of whom had osteogenic sarcoma (OGS). A number of cases were referred from other institutions, where they had been considered inoperable because of extensive or recurrent disease. Using lateral thoracotomies, laser technique with minimal parenchymal excision, and thin gloves for palpation, aggressive metastasectomy was carried out. A mean of 3.1 thoracotomies were performed, with an average of 10.6 nodules resected per thoracotomy. Operative morbidity and mortality were minimal. Evaluation of potential prognostic factors revealed no statistically significant survival difference on the basis of disease-free interval (DFI), number of nodules resected, number of thoracotomies, or size of largest nodule resected. There was a clear trend toward decreased survival of patients with larger nodules (> 2 cm), but because of the small number of patients in this group, no firm conclusions can be drawn. Five-year survival was 49% for the study group as a whole, and 39% for the OGS patients. Aggressive surgical resection of pulmonary metastases from bone and soft-tissue sarcoma should be

considered when there is control of local disease, no evidence of extrapulmonary metastasis, and adequate postresection pulmonary reserve. The presence of bilateral, extensive, or recurrent disease is not a contraindication to thoracotomy. Resection of multiple nodules or extensive bilateral disease appears to prolong survival of patients with metastatic sarcoma, as compared to historical controls. Similarly, repeated thoracotomy and resection for patients with recurrent metastases may also prolong survival.

Evolution in the treatment of osteogenic sarcoma (OGS) over the past few decades has resulted in markedly improved survival. Changes have occurred in surgical management of the primary tumor, adjuvant chemotherapy, and surgical treatment of metastatic deposits. Similar alterations in the management of other bone and soft-tissue sarcomas have occurred.

Pulmonary metastases are the primary cause of death in patients with bone and soft-tissue sarcoma. Recognition that occult microfoci of disease may be present at initial diagnosis prompted successful intervention with neoadjuvant chemotherapy. This has reportedly extended the disease-free interval (DFI), decreased the number of pulmonary metastases, and prolonged survival.<sup>1,4,10,18</sup> However, other reports have not substantiated these results.<sup>7,12</sup>

Several studies have identified factors that could be used as prognostic indicators: tumor

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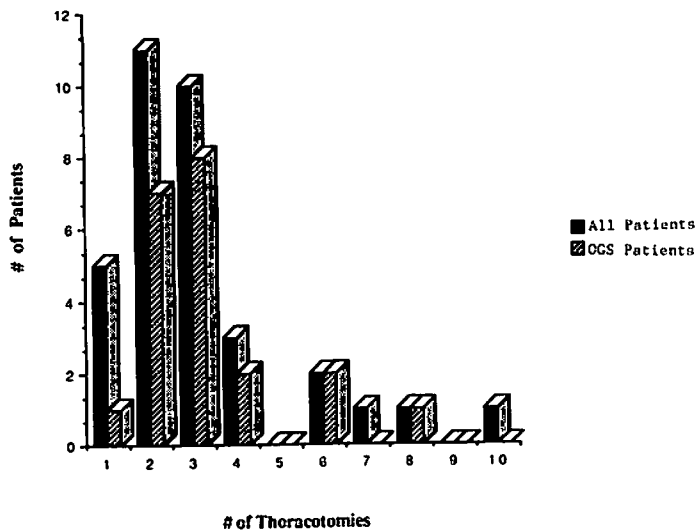


FIG. 1. Number of thoracotomies performed per patient for study group as a whole and for osteogenic sarcoma (OGS) patients only.

doubling time (TDT), number of lesions removed, DFI, unilateral versus bilateral disease, and number of lesions seen on full-lung tomography.<sup>8,15,16,19,24</sup> Some authorities feel these are sufficiently accurate predictors to exclude selected patients from consideration for thoracotomy and resection of metastases.<sup>11</sup>

In recent years, it has been suggested that an aggressive operative approach toward pulmonary metastasis can improve survival rates for patients with OGS and other sarcomas.<sup>3,17,20</sup> However, patients with extensive, bilateral, or recurrent metastatic deposits are often considered inoperable. The authors reviewed the results of an aggressive surgical and chemotherapeutic approach to extensive, or recurrent, pulmonary sarcoma metastases and attempted to identify and evaluate specific predictors of survival after resection of metastatic pulmonary lesions.

#### MATERIALS AND METHODS

From January 1977 to April 1989, 106 thoracotomies were performed on 34 patients for resection of sarcoma metastasis, for a mean of 3.1 thoracotomies per patient (Fig. 1). The patients had a variety of primary tumors, mostly OGS (Table 1). Since the OGS patients constituted the largest homogeneous group, they were also reviewed separately (Table 2).

Treatment of bone and soft-tissue sarcoma at the authors' institution is multidisciplinary. After resection of the primary tumor, combination chemotherapy was given (usually consisting of doxorubicin hydrochloride [Adriamycin], cisplatin, vincristine, and methotrexate), and the patients were followed with serial chest roentgenograms every two months for a two-year period. If pulmonary metastasis was evident on the plain roentgenographic studies, a computed tomography (CT) scan was obtained. Patients with suspicious findings were considered candidates for thoracotomy. The following criteria were used to decide operability: (1) control of the primary disease, (2) adequate postresection pulmonary reserve, and (3) absence of extrapulmonary, metastatic disease. The presence of bilateral or extensive pulmonary disease on preoperative radiographs was not a reason for exclusion from thoracotomy.

Only patients who were treated with thoracotomy for pulmonary sarcoma metastases were in-

TABLE 1. Pathology of Resected Nodules

Primary Tumor	Number
Osteogenic sarcoma	21
Ewing's sarcoma	6
Malignant fibrous histiocytoma	4
Rhabdomyosarcoma	1
Adamantinoma	1
Hemangiopericytoma	1
Total	34

TABLE 2. Comparison of OGS to All Patients

Parameter	All Patients	OGS Patients
Sex	male, 20; female 14	male, 13; female 8
Age (mean)	23 years	17 years
Primary treatment	12	11
Limb salvage		
Amputation	14	10
Other	8	0
Primary site of origin	17	12
Femur		
Tibia/fibula	6	4
Humerus	3	3
Pelvis	3	1
Other	5	0

cluded in this study. Patients with bilateral disease received staged thoracotomy, with a one- to two-week interval between operations. Of the 34 patients, 16 (48%) received staged bilateral thoracotomies. Median sternotomy was not used, since this limits palpation of the posterior hilar regions of the lungs.

At operation, the lungs were sequentially and thoroughly palpated in the inflated and deflated state by the surgeon and first assistant. Thin gloves were utilized so pinpoint lesions would be felt. Any suspicious lesions were resected, with a minimum of normal surrounding pulmonary tissue. Automatic stapling devices were avoided, since they tend to sacrifice more pulmonary parenchyma than does manual nodule resection. Moreover, with the large numbers of nodules found in these patients, respiratory insufficiency might occur and preclude further thoracotomies. Lateral thoracotomy was important in identification and accurate removal of nodules in the posterior segments. It was observed in patients sent from other institutions, who had sternal splits for bilateral resection of nodules, that a number of posterior nodules were missed. Pulmonary defects following excisions were closed in two running layers with absorbable suture material. Early in the study, resection was performed by cutting out the nodules with scissor technique. In the last four years, however, the use of the carbon dioxide or the neodymium doped yttrium aluminum garnett crystal (YAG) laser has allowed a much more exact anatomic dissection. One can protect the segmental vessels and bronchi, seal lymphatics, and minimize blood loss. This technique was a very important addition to this series. Very small or pinpoint

nodules were removed in a similar fashion. The vast majority of the nodules were subpleural, and thus easily removable without extensive resection. All thoracotomies were performed under the direct supervision of the senior author. It is interesting that despite the presence of only three or four nodules on many CT scans, up to 50 or more nodules were found and removed in a number of these patients.

Follow-up evaluation was available in 32 patients, with a mean of 3.43 years and a range of 0.46 to 21.2 years. Of the 34 patients, 18 were alive at the study's conclusion. Survival data was evaluated with life-table analysis. Comparison between two groups was with the Wilcoxon's two-sample test. Values of  $p \leq 0.05$  were considered statistically significant.

### RESULTS

Operative morbidity and mortality were minimal. There were two deaths in the perioperative period, neither from complications related to the surgery. The most common sources of morbidity were related to the chest tube: persistent air leak, pneumothorax, or persistent pleural effusion. These were infrequent, minor complications that did not prolong the hospital course.

The authors attempted to identify parameters that might correlate with survival, including DFI, number of tumor nodules removed, number of operations, and size of the largest nodule removed (Table 3).

The mean DFI was 19.3 months for all patients, and 12.3 months for the OGS patients. Patients were subdivided as follows: (1) DFI less than or equal to six months, (2) DFI less

TABLE 3. Parameter Comparison of OGS to All Patients

Parameter	All Patients	OGS Patients
Disease-free interval	580 days	369 days
No. of nodules resected	10.6	12.2
No. of thoracotomies (mean)	3.1	3.2
Survival after 1st thoracotomy	3.4 years	3.8 years

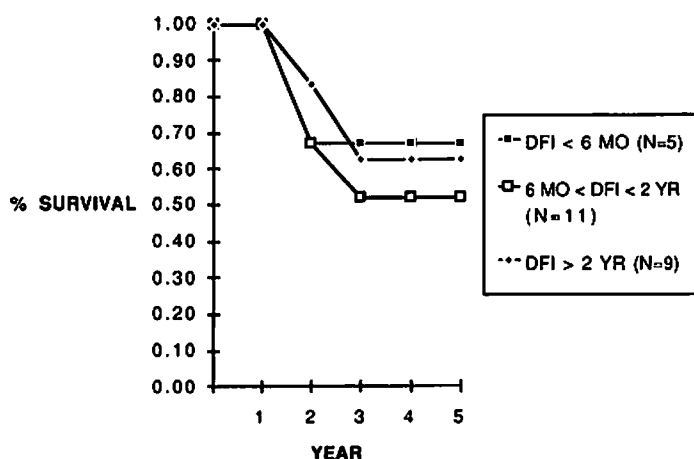


FIG. 2. For patients with differing disease-free intervals, percent survival per year after initial thoracotomy. There was no statistically significant difference between the groups.

than or equal to two years, and (3) DFI greater than two years. No statistically significant difference in survival was found (Fig. 2).

Patients were categorized by the number of tumor nodules resected at thoracotomy, depending on whether fewer than three (inclusive) or more than three nodules were resected. Although there was a trend toward improved survival in patients with fewer than three nodules resected, it was not statistically significant (Fig. 3). The overall mean number of resected nodules per thoracotomy was 11. The mean number of nodules resected per thoracotomy for the OGS patients was 12.

Patients underwent from one to ten thoracotomies, with an overall average of 3.1 oper-

ations per patient (Fig. 1). Patients were divided into two groups: those who had fewer than three and more than three thoracotomies. No relationship could be demonstrated between the number of thoracotomies performed and survival (Fig. 4).

The resected nodules were measured, and the cross-sectional diameter of the largest nodule was recorded. The overall mean largest nodule size was 1.97 cm in diameter, and 1.67 cm for the OGS group. The patients were divided into three groups: (1) largest nodule less than or equal to 1 cm, (2) largest nodule less than or equal to 2 cm, and (3) largest nodule greater than 2 cm. There was a clear trend toward decreased survival in the

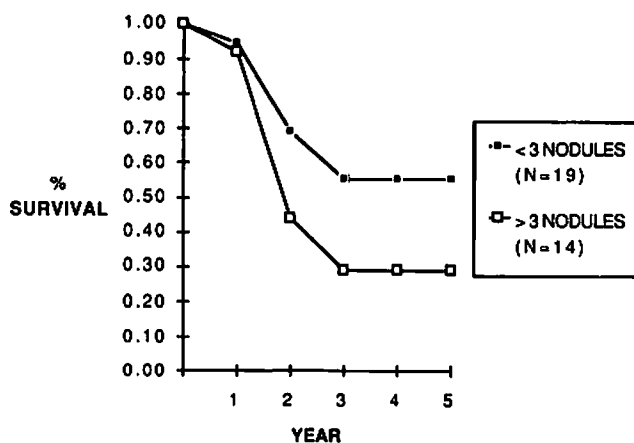
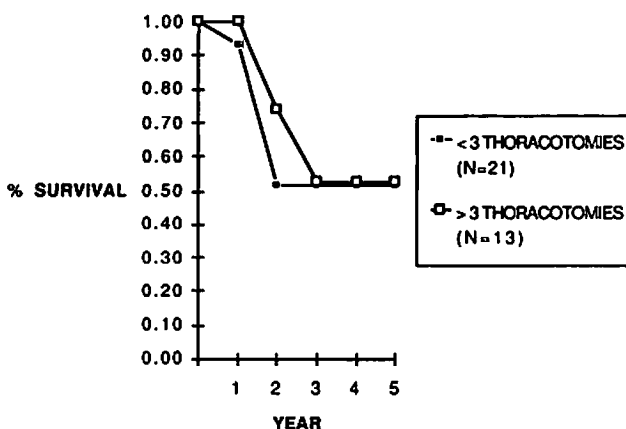


FIG. 3. For patients with less than or equal to three or more than three nodules resected, percent survival per year after initial thoracotomy. There was no statistically significant difference between the groups.

FIG. 4. For patients undergoing less than or equal to three or more than three thoracotomies per year after initial thoracotomy. There was no statistically significant difference between the groups.



patients with nodules larger than 2 cm, but it was not statistically significant (Fig. 5).

Survival curves were calculated for the study group as a whole, and for the OGS patients (Fig. 6). The overall five-year survival was 49%; for the OGS patients, 39%. These differences were not statistically significant.

### DISCUSSION

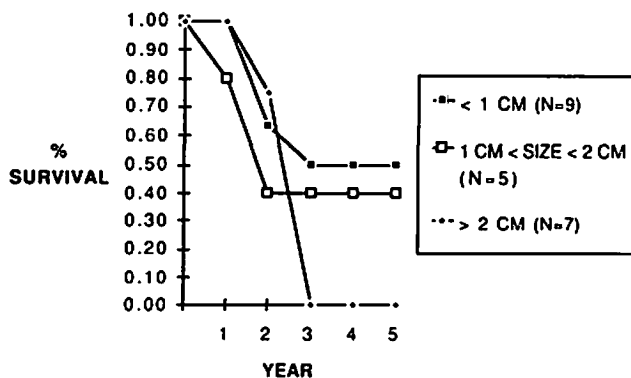
Historically, untreated pulmonary metastases from OGS were associated with a two-year survival of less than 20%.<sup>5</sup> Several studies have documented improved survival with adjuvant chemotherapy and surgical resection, with five-year survival rates ranging from 22% to 50%. However, many of these studies excluded patients with extensive disease (multiple nodules) as inoperable.<sup>2,5,6,12-14,17,19,20,23,25</sup> A number of patients

in this study were referred from other institutions that had refused operation on the basis of extensive or recurrent disease.

Although a more aggressive surgical approach to pulmonary sarcoma metastases is now widely accepted, some authorities have advocated limiting metastasectomy to select groups, *e.g.*, patients with fewer than six nodules, a long DFI, or slow TDTs.<sup>9,11</sup> These and other parameters have been found to correlate with improved survival.

An extremely aggressive surgical approach for pulmonary OGS metastasis is warranted. No parameters have been clearly identified that are accurate enough predictors of outcome to guide patient selection for operation. In the present series, survival for patients with fewer than three nodules was marginally better but not statistically significant (Fig. 3). Others have noted similar findings.<sup>13,22</sup> For

FIG. 5. For patients categorized by the size of the largest nodule resected, percent survival per year after initial thoracotomy for resection of metastases. Despite a trend toward poorer survival for patients with larger nodules (more than 2 cm), there was no statistically significant difference between the groups.



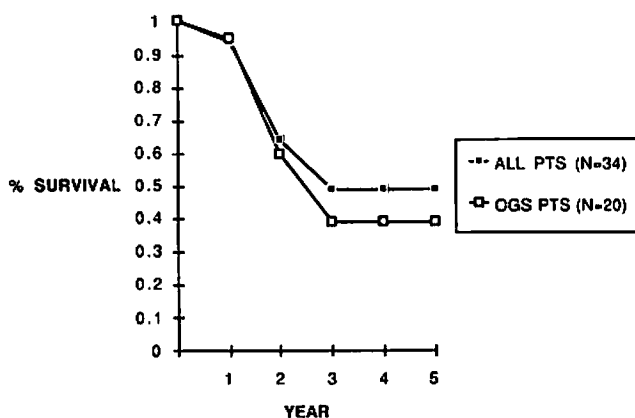


FIG. 6. For patients as a whole versus OGS patients, percent survival per year after initial thoracotomy. The five-year survival rate for the study group as a whole was 49%; for the OGS patients, 39%.

this reason, the authors' policy is to explore any patient with isolated pulmonary metastasis from sarcoma, regardless of the extent of disease seen on preoperative radiographic studies. The authors have removed as many as 80 to 100 nodules during a single thoracotomy.

Multiple thoracotomies to resect recurrent disease have been identified by some authors as an indicator of poor outcome.<sup>7,23</sup> The authors were unable to demonstrate any difference in survival for patients treated with fewer than three thoracotomies compared to those with more than three thoracotomies (Fig. 4). This seems to support multiple thoracotomies for recurrent metastatic disease. Others report similar findings.<sup>11,13</sup>

One argument against resection of widespread metastatic deposits is the risk of leaving the patient with inadequate pulmonary reserve. Automatic stapling devices remove significant amounts of normal surrounding pulmonary parenchyma with each nodule. For this reason, the authors eschew these devices in favor of limited nodulectomy, with hand-sewn closure of the pulmonary defect. A minimum of functional pulmonary reserve is lost with this technique. The CO<sub>2</sub> or YAG laser also helps conserve pulmonary tissue, allows minimal blood loss, and preserves segmental structures.

Tumor necrosis in resected pulmonary nodules has been reported to be an indicator

of improved prognosis.<sup>24</sup> Tumor necrosis was observed in only four of 34 patients at the initial thoracotomy. Unfortunately, one patient was lost during the follow-up interval. The other three patients had prolonged survival (a mean of 10.4 years). Although no definitive conclusions can be drawn from this small number of patients, the implication is that nodule necrosis may indicate an improved response to chemotherapy.

Although there was a trend toward increased survival with a DFI of more than two years, there was no statistically significant correlation. The literature is equally divided on this point; several papers report a significant relationship between DFI and survival, whereas others do not.<sup>5,17,21,22</sup> Since a shorter DFI might indicate a more virulent neoplasm, such an association is at least theoretically attractive. Tumor doubling time, another variable related to tumor virulence that has also been reported to correlate well with outcome, was not reviewed in this series.<sup>11</sup>

The size of the resected nodules has been suggested as a prognostic indicator. Larger nodules should represent faster tumor growth, since all (even asymptomatic) patients were evaluated roentgenographically at fixed intervals. The data did, in fact, show decreased survival of patients with nodules smaller than 2 cm but it was not statistically significant.

In summary, overall survival was 55% after

pulmonary resection for sarcoma metastasis, with an overall five-year survival of 49%. There was no statistically significant survival difference on the basis of the number of thoracotomies performed, number of nodules resected, size of nodules, or DFI. An aggressive approach using lateral thoracotomies and laser technique for surgical resection of pulmonary sarcoma metastases is warranted. Indications for resection of pulmonary sarcoma metastases include the presence of all of the following: (1) control of the primary disease, (2) ability to preserve an adequate amount of functional pulmonary tissue, and (3) absence of extrapulmonary metastatic deposits. The presence of extensive, bilateral, or recurrent metastatic deposits should not be a contraindication to thoracotomy.

#### REFERENCES

1. Bacci, G., Avella, M., and Picci, P.: Metastatic patterns in osteosarcoma. *Tumori* 74:421, 1988.
2. Beattie, E. J.: Surgical treatment of pulmonary metastases. *Cancer* 54:2729, 1984.
3. Blasier, J., Mayaba, I., and Ferguson, C.: Metastatic osteosarcoma and multiple lung resection. A case report. *J. Bone Joint Surg.* 68A:748, 1986.
4. Ettinger, L. J., Douglass, H. O., and Mindell, E. R.: Adjuvant adriamycin and cisplatin in newly diagnosed, nonmetastatic osteogenic sarcoma of the extremity. *J. Clin. Oncol.* 4:353, 1984.
5. Flye, M. W., Woltering, G., and Rosenberg, S. A.: Aggressive pulmonary resection for metastatic soft tissue sarcomas. *Ann. Thoracic Surg.* 37:123, 1984.
6. Goorin, A. M., Delorey, M. J., and Lack, E. E.: Prognostic significance of complete surgical resection of pulmonary metastases in patients with osteogenic sarcoma: Analysis of 32 patients. *J. Clin. Oncol.* 2:425, 1984.
7. Han, M., Telander, R. L., and Pairolero, P. C.: Aggressive thoracotomy for pulmonary metastatic osteogenic sarcoma in children and young adolescents. *J. Pediatr. Surg.* 16:928, 1981.
8. Huth, J. F., Holmes, E. C., Vernon, S. E., Callery, C. D., Ramming, K. P., and Morton, D. C.: Pulmonary resection for metastatic sarcoma. *Am. J. Surg.* 140:9, 1980.
9. Ishihara, T., Kikuchi, K., Ikeda, T.: Metastatic pulmonary disease: Biologic factors and modes of treatment. *Chest* 63:227, 1973.
10. Jaffe, N., Frei, E., III, and Traggis, D.: Adjuvant methotrexate and citrovorum-factor treatment of osteogenic sarcoma. *N. Engl. J. Med.* 291:990, 1974.
11. Joseph, W. L., Morton, D. L., and Adkins, P. C.: Prognostic significance of tumor doubling time in evaluating operability in pulmonary metastatic disease. *J. Thorac. Cardiovasc. Surg.* 61:23, 1971.
12. Marcove, R. C., Martini, N., and Rosen, G.: The treatment of pulmonary metastasis in osteogenic sarcoma. *Clin. Orthop.* 111:65, 1975.
13. Martini, N., Huvos, A. G., and Mike, V.: Multiple pulmonary resections in the treatment of osteogenic sarcoma. *Ann. Thoracic Surg.* 12:271, 1971.
14. Meyer, W. H., Schell, M. J., and Kumar, A. P. M.: Thoracotomy for pulmonary metastatic osteosarcoma: An analysis of prognostic indicators of survival. *Cancer* 59:374, 1987.
15. Morrow, C. E., Vassilopoulos, P., and Grage, T. B.: Surgical resection for metastatic neoplasms of the lung: Experience at the University of Minnesota Hospitals. *Cancer* 45:2981, 1980.
16. Morton, D. L., Joseph, W. L., Ketcham, A. S., Geehoed, G. W., and Adkins, P. C.: Surgical resection and adjunctive immunotherapy for selected patients with multiple pulmonary metastasis. *Ann. Surg.* 178:360, 1973.
17. Pastorini, U., Valente, M., and Gasparini, M.: Lung resection as salvage treatment for metastatic osteosarcoma. *Tumori* 74:201, 1988.
18. Pratt, C., Shanks, E., and Hustu, O.: Adjuvant multiple drug chemotherapy for osteosarcoma of the extremity. *Cancer* 39:51, 1979.
19. Putnam, J. B., Roth, J. A., Wesley, M. N., Johnston, M. R., and Rosenberg, S. A.: Survival following aggressive resection of pulmonary metastasis from osteogenic sarcoma: Analysis of prognostic factors. *Ann. Thorac. Surg.* 36:516, 1983.
20. Rodgers, B. M., Talbert, J. L., and Alexander, J. A.: Pulmonary metastasis in childhood sarcoma. *Ann. Thoracic Surg.* 29:410, 1980.
21. Roth, J. A., Putnam, J. B., and Wesley, M. N.: Differing determinants of prognosis following resection of pulmonary metastases from osteogenic and soft tissue sarcoma patients. *Cancer* 55:1361, 1985.
22. Schaller, R. T., Haas, J., and Morgan, A.: Improved survival in children with osteosarcoma following resection of pulmonary metastases. *J. Pediatr. Surg.* 17:546, 1982.
23. Spanos, P., Payne, W. S., and Ivins, J. C.: Pulmonary resection for metastatic osteogenic sarcoma. *J. Bone Joint Surg.* 58A:624, 1976.
24. Takita, H., Edgerton, F., Karakousis, C., Geehoed, G. W., and Adkins, P. C.: Surgical Management of metastases to the lung. *Surg. Gynecol. Obstet.* 152:191, 1981.
25. Telander, R. L., Pairolero, P. C., and Pritchard, D. J.: Resection of pulmonary metastatic osteogenic sarcoma in children. *Surgery* 84:335, 1978.

# Diagnostic Imaging of Osteosarcoma

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The diagnosis, treatment planning, and follow-up evaluation of osteosarcoma rely heavily on a variety of imaging techniques. Plain roentgenography, radionuclide bone scanning, computed tomography, and magnetic resonance imaging play important roles in defining local tumor extent, detecting metastatic disease, and monitoring for recurrent tumor. Invasive studies such as angiography are now rarely necessary. In the future, newer imaging modalities, including positron emission tomography, can be expected to become important tools for evaluation of these tumors.

The diagnosis of osteosarcoma is usually founded on clinical history and plain roentgenographic findings and is confirmed with biopsy. Once the diagnosis has been established, decisions regarding medical and surgical management rely heavily on the results of a variety of imaging studies.

Radionuclide bone scanning with technetium 99m methylene diphosphonate (<sup>99m</sup>Tc-MDP) assists in the detection of osseous metastatic lesions. Chest roentgenographs and computed tomography (CT) of the chest are useful tools for detecting pulmonary metastatic disease. CT and magnetic resonance imaging (MRI) are valuable methods of defining the osseous and soft-tissue extent of the tumor and determining their relationship to major neurovascular structures and adjacent joints. Comparison of images obtained

before and following preoperative chemotherapy may provide prognostic information by depicting tumor response to therapy. Following surgery, plain roentgenography, radionuclide bone scanning, and cross-sectional imaging may all be used to identify local recurrence and metastatic disease.

In this article, the authors discuss the preoperative and postoperative imaging evaluation of the patient with osteosarcoma. The concepts that are discussed reflect an ongoing collaborative effort between the sections of musculoskeletal radiology and oncologic orthopaedic surgery at the authors' institution.

## PLAIN ROENTGENOGRAPHY

Whereas other imaging modalities may better depict the bone and soft-tissue extent of a lesion, plain roentgenography is the key imaging modality for its diagnosis. This is especially true for osteosarcoma.

Several classification systems of osteosarcoma have been proposed. The most common reflects the predominant type of tissue in the tumor as well as its location within the bone.<sup>14</sup> Primary osteosarcomas may be classified as intramedullary (central) or juxtacortical. The predominant histologic type may be reflected in its roentgenographic appearance. Since most osteosarcomas have a mixed histologic pattern, their roentgenographic appearance combines sclerotic and lytic changes. Some osteosarcomas are primarily composed of mineralized osteoid and are sclerotic (Fig. 1). For others, in which unmineralized cartilage, spindle cells, histio-

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